REMARKS

In the previously filed Response to Restriction Requirement, Applicant elected, with traverse, the invention of Group II, drawn to a composition comprising a surfactant associated with a bioactive component and a shell surrounding the bioactive component and surfactant, wherein the shell comprises at least one biocompatible polymer that provides specific cellular or tissue uptake that is a biocompatible polymer. The Examiner made the restriction final.

Per Applicant's 5/24/2006 request, claims 68-86, 103-109, 111-116, 118, 119, 122-124, 126, and 127 are withdrawn from further consideration. The Examiner disregarded Applicant's request for withdrawal of claim 66, correctly noting that the request for withdrawal of claim 66 was a typographical error on the part of Applicant. The Examiner has withdrawn claims 95, 97-100, and 102 from further consideration as being drawn to nonelected species. Accordingly, in the Office Action dated 6/14/2006, claims 66, 67, 87-94, 101, 133, and 134 were examined.

In the instant Amendment and Response, Applicant has amended claims 66, 94, 133, and 134. Applicant has added new claims 135-136, which are drawn to the elected species. Amendments to claim 66 are in the nature of minor clarifying amendments. Support for the instant claim amendments of claim 94 and claim 133, 134, and new claims are discussed herein below. Reconsideration of the Examiner's rejections is respectfully requested in view of the claim amendments and following arguments.

DOUBLE PATENTING

The Examiner has provisionally rejected claims 66, 67, 87, 88, 90, 92-94, 101, 133, and 134 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2 and 8 of copending Application no. 10/378,044.

The Examiner has also provisionally rejected claims 66, 67, 87, 88, 90, 92-94, 101, 133, and 134 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10 and 13 of copending Application No. 10/958,999.

The Examiner has also rejected claims 66, 67, 87-94, 101, 133, and 134 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 29 and 42 of U.S. Patent No. 6,632,671.

Applicant acknowledges these rejections, and will address these rejections once all other matters relating to patentability have been resolved.

ADVISEMENT

The Examiner advised Applicant (page 10 of Office Action) that should claim 87 be found allowable, claim 90 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. The Examiner contends that claim 90 recites several species of non-ionic species.

Applicant traverses this potential objection. Applicant also requests that Applicant's argument be considered for newly added claim 135, in the event that the Examiner would raise the same potential objection to claim 135. The Examiner is correct that claim 90 recites several species of non ionic surfactant, namely, cetyl alcohol, 2, 4, 7, 9-tetramethyl-5-decyn-4, 7-diol, molecules containing an acetylenic diol portion, and blends of 2, 4, 7, 9-tetramethyl-5-decyn-4, 7-diol. New claim 135 recites 2, 4, 7, 9-tetramethyl-5-decyn-4, 7-diol, molecules containing an acetylenic diol portion, and blends of 2, 4, 7, 9-tetramethyl-5-decyn-4, 7-diol.

Applicants note, however, that claim 87 recites non-ionic surfactants as a genus which includes the species recited by the Applicant. See Specification, page 13, lines 26-32. Only a subset of the non-ionic surfactant genus as described by the Applicant is recited in claims 90 and 135. In claim 90, species recited include cetyl alcohol, 2, 4, 7, 9-tetramethyl-5-decyn-4, 7-diol, molecules containing an acetylenic diol portion, and blends of 2, 4, 7, 9-tetramethyl-5-decyn-4, 7-diol. Claim 135 is similar to claim 90 except that claim 135 omits cetyl alcohol. Accordingly, Applicant submits that the scope of claims 90 and 135 are different in scope from claim 87, for the reason that claims 90 and 135 recite specific species of non-ionic surfactants, while claim 87 recites non-ionic surfactant as a genus. Reconsideration is respectfully requested.

CLAIM REJECTIONS UNDER 35 U.S.C. § 102(e)

The Examiner has rejected claims 66, 67, 87, 88, 90-92, 94, and 101 as being anticipated by Unger, E.C. et al. (U.S. Patent No. 6,139,819). The Examiner contends that Unger et al. teach particles comprising a core provided by paramagnetic contrast agents that are bound to proteinaceous macromolecules, a surfactant molecule, which is associated with the bioactive component, and a biocompatible polymer that ensures substantial particle encapsulation, wherein the biocompatible particle can be a protein and wherein the biocompatible polymer provides targeting ligands for targeted delivery to cells or tissues. The Examiner also contends that Unger

et al. teach that the particles have a size of about 30 nm, the particles can comprise a combination of two or more surfactants, a biocompatible oil, and a water miscible solvent. The Examiner contends that Unger et al. teach all of the limitations of the instant claims and accordingly the claimed invention is anticipated.

Before turning to a discussion of the rejections, Applicant first respectfully disputes the Examiner's statement that Unger et al. teaches "a biocompatible polymer that ensures substantial particle encapsulation (i.e. the biocompatible polymer forms a shell that surrounds the association between the bioactive component and the surfactant." (Office Action, sentence spanning pages 10-11). Applicant respectfully submits that contrary to the Examiner's assertion, Unger et al. does not teach encapsulating a bioactive component and a surfactant. Instead, the use of "encapsulation" by Unger et al., (Col 30, lines 18-32) is only in reference to gases or gaseous precursors. The actual quote from Unger et al. reads: "assuring substantial encapsulation of the gases or gaseous precursors." Thus, Unger et al. does not teach encapsulation of a bioactive component/surfactant as does Applicant; instead, Unger et al. teach encapsulation of a gas or gaseous precursor. Accordingly, in contrast to the Examiner's assertion, Applicant respectfully submits that Unger et al. does not teach a biocompatible polymer that ensures substantial encapsulation of bioactive component and the surfactant. Correction is hereby requested.

Applicant traverses the Examiner's rejection. Applicant's main arguments can be summarized as follows. First, Applicant contends that the claimed invention is directed to a narrow range of particle sizes, and the reference teaches a broad range, and accordingly, it is reasonable to conclude that Applicant's narrow range is not disclosed with "sufficient specificity" in Unger et al. to constitute an anticipation of the claims as claimed in claims 66, 67, 87, 88, 90-92, 94, and 101 and new claims 135-136. Second, Applicant contends that the portion of Unger et al.'s disclosure directed to particles of less than 50 nm is not an enabling disclosure, since Unger et al.'s disclosure with respect to sub-50 nm particles does not disclose methods to produce particles of that size and which incorporate a bioactive component, a surfactant having an HLB value of less than about 6.0 units ("surfactant"), and a biocompatible polymer with specific cellular or tissue uptake function, as claimed in claims 66, 67, 87, 88, 90-92, 94, and 101 and new claims 135-136. Third, Applicant contends that not all of the elements of the instant claims are disclosed in Unger et al., namely, that the surfactant vesicles taught by Unger are

limited to bilayers, while the instant particles as presently claimed (made up of a bioactive component core, a surfactant, and biocompatible polymer with specific cellular or tissue uptake function, having an average diameter of less than about 50 nanometers) comprise monolayer surfactants, as claimed in claim 135. These arguments will be explained in more detail hereinbelow.

(a) *Assuming, arguendo, that all "elements" are disclosed in the reference, the disclosure of Unger et al. does not rise to the level of an anticipation*

In this argument, Applicant will discuss how the claimed invention is directed to a narrow range of particle sizes, whereas the reference teaches a broad range, and accordingly, it is reasonable to conclude that the narrow range is not disclosed with "sufficient specificity" to constitute an anticipation of the claims.

There are a number of situations when "all the elements" of an instant claim appear to be disclosed, legally, the disclosure does not constitute"anticipation" under current case law. Even if it is assumed, *arguendo*, that all elements are disclosed within Unger et al., (which Applicant does not admit), Applicant contends that such disclosures are not sufficient for anticipation. In Applicant's first argument, Applicant discusses MPEP § 2131.03(II) relating to disclosure of ranges, discussing situations where prior disclosure of a range that "touches" or "overlaps" the claimed range does not anticipate the claimed range.

The MPEP notes at § 2131.03(II) that "[w]hen the prior art discloses a range which touches or overlaps the claimed range, but no specific examples falling within the claimed range are disclosed, a case by case determination must be made as to anticipation." Applicant notes that in Unger et al., the disclosed size range of Unger's vesicles are between 30 nanometers and about 100 micrometers, apparently overlapping Applicant's claimed size (see Claim 66, 67, 87, 88, 90, 92-94, 101, 133-136) having an average diameter of less than about 50 nanometers. Applicant, however, upon careful review of the Examples section of Unger et al., submits that none of the examples in Unger et al. disclose a vesicle of less than about 200 nanometers. Accordingly, the instant situation falls squarely within the scope of this section of the MPEP, necessitating that the Examiner undertake a determination as to anticipation specific to this particular case.

The MPEP then continues (at § 2131.03(II)), "[i]n order to anticipate the claims, the claimed subject matter must be disclosed in the reference with 'sufficient specificity to constitute an anticipation under the statute.' What constitutes a 'sufficient specificity' is fact-dependent. If the claims are directed to a narrow range, and the reference teaches a broad range, . . . it may be reasonable to conclude that the narrow range is not disclosed with 'specific specificity' to constitute an anticipation of the claim," *citing Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006). Again, this case falls squarely within the confines of the *Atofina* case and this section of the MPEP. The disclosed size range of Unger et al.'s vesicles are between 30 nanometers and about 100 micrometers. The range taught by Unger et al. is thus between 30 nm and 100 micrometers and is exceedingly broad. The two ends of the Unger et al. range are different by three to four orders of magnitude or greater than 3000-fold.

In contrast, the instant application's claim 66 states that Applicant's particles have an average diameter of less than about 50 nanometers. It is noted that the ranges recited by Applicant are an average, or mean, and that many of the particles will have an average diameter of less than 50 nm, further distinguishing Applicant's range from the range of Unger, et al. Applicant's claimed range (i.e., less than 50 nm) overlaps only about 20 nm, at most, out of Unger's disclosed range of 3000 nm, fitting the instant case squarely within the confines of the *Atofina* case. In fact, in *Atofina*, the court held that a reference temperature range of 100-500 degrees C did not describe the claimed range of 350-450 degrees C with sufficient specificity to be anticipatory. *Id.* at 1000. It can clearly be seen that the ranges disclosed in the instant claims and in Unger et al. overlap far less than the ranges in *Atofina,* strengthening Applicant's argument that the Federal Circuit's finding of no anticipation in *Atofina* is applicable in this case.

In *Atofina*, the court held that the disclosure in the prior art was only that of a range, not a specific temperature in that range, and "the disclosure of a range is no more a disclosure of the end points of the range than it is of each of the intermediate points." *Atofina*, 441 F.3d. The court concluded that the prior art, thus, "does not disclose a specific embodiment of the claimed temperature range." *Id.* Similarly, Applicant's claimed size, i.e., an average diameter of less than about 50 nanometers, is a specific species of all possible size ranges of Applicant's particles. Importantly, the size species claimed by Applicant is the size cutoff for efficient caveolae uptake of Applicant's particles into cells, allowing for avoidance of destruction of the particles by lysosomes within the cells. (See Example 2 of the instant specification.) In contrast, Unger et

al. provides only the broad range with no similar description of his stated 30 nm threshold. Unger et al. does not disclose a claimed range, as was the case in *Atofina*, and thus Unger et al.'s disclosure is not an anticipation of Applicant's claim, which recites an average diameter of less than about 50 nanometers.

Reconsideration of the anticipation rejection for claims 66, 67, 87, 88, 90-92, 94, and 101 and allowance of new claims 135-136 is respectfully requested.

(b) *The portion of Unger et al.'s disclosure directed to particles of less than 50 nm is not an enabling disclosure, since Unger et al.'s disclosure with respect to sub-50 nm particles does not disclose methods to produce particles of that size*

MPEP § 2121.01 states that "in determining that quantum of prior art disclosure which is necessary to declare an applicant's invention 'not novel' or 'anticipated' within Section 102, the stated test is whether a reference contains an 'enabling disclosure,'" *citing In re Hoeksema*, 399 F.2d 269 (CCPA 1968). Further cases elaborate on this concept. In 2003, the Federal Circuit stated, "mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation." *Elan Pharm. Inc. v. Mayo Found. For Med. Educ. & Research*, 346 F.3d 1051, 1054 (Fed. Cir. 2003).

In the instant case, Applicant's claims 66, 67, 87, 88, 90-92, 94, and 101 and new claims 135-136 are directed towards particles (made up of a bioactive component core, a surfactant, and polymer with specific cellular or tissue uptake function, having an average diameter of less than about 50 nanometers). Of note, the particles have an average diameter of less than about 50 nanometers. Unger et al. contain disclosure of particles having a diameter of between 30 nanometers and about 100 micrometers. However, as will be discussed more fully hereinbelow, Applicant submits that the portion of the Unger et al. disclosure with respect to sub-50 nm particles comprising a bioactive component core, a surfactant, and polymer particles is <u>not</u> an enabling disclosure, for the reason that achieving such sub-50 nm sized particles from the disclosure of Unger et al. would require undue experimentation on the part of a skilled artisan. Applicant presents the following discussion and also submits a Declaration under 37 CFR § 1.132 as factual evidence to rebut operability/enablement of Unger et al. with respect to sub-50 nm sized particles.

As discussed above, the Unger *et al.* specification is directed primarily towards the preparation of lipid compositions comprising vesicles, particularly liposomes, containing gases or low-boiling liquids as gaseous precursors. See issued claims; Col. 6, lines 22-28. Accordingly, Unger et al. are not disclosing new methods for formulating lipid compositions such as vesicles and liposomes; rather, Unger et al. is adapting previously known methods for formulating lipid compositions to further include gases and/or bioactive components. Unger et al. discloses only art-known methods for creating the Unger et al. lipid compositions (which further comprise a bioactive component or gas/gaseous precursor). Applicant contends that such art-known methods disclosed by Unger et al. do not result in the claimed, inventive sub-50 nm average diameter particles.

Applicant has carefully reviewed the Examples section of Unger, et al. Applicant submits that none of the examples in Unger et al. disclose a vesicle of less than 200 nanometers (i.e., less than 0.2 μm or microns). See, for example, prophetic Example 39A (Col 112, line 54) which cites a 200 nm particle of sonicated, cross-linked albumin. Also, for the method given in prophetic Example 11, (milling to entrain gas into polymer with a high HLB surfactant followed by divalent cation precipitation for stabilization) no size is described for the resultant polymer vesicle. Applicant notes, however, that Example 11 refers to and appears to be taken almost verbatim from Langer et al., U.S. Patent No. 5,487,390, for the method of making the vesicles. Langer et al. reports larger particles of 3 – 15 μm.

As stated in Applicant's Declaration, Applicant notes that Unger et al.'s preparatory methods for micelles, listed in Column 60, starting at line 50, cite conventional methods that do not teach Applicant's particles, as claimed. These conventional methods for preparation of bile salt micelles include suspension of the lipid in organic solvent followed by evaporation of the solvent, resuspension in aqueous medium, sonication, and centrifugation, result in aggregated particles of greater than 50 nm in average diameter. References Shinoda et. al, *Colloid Chemistry*, (1963), ppg. 1-88 and Fendler et. al, *Catalysis in Micellar and Macromolecular Systems* (Col. 60, lines 60-66) describe the physicochemical characterization of micelles and particularly the varieties of geometries that micelles can take and do not disclose methods for making micelles or particles. Unger et al.'s additional references (El-Ghorab et. al, *BBA*, (1973) v. 306, ppg. 58-66 and Canfield et. al, *Meth Enzymol* (1990) v.189, ppg. 418-22) describe the incorporation of ß-carotene both with and without retinol into micelles based on bile salts as

surfactants. As summarized by Unger et al. in Col 60, line 54, these citations describe a method consisting of 1) dissolution of ß-carotene into a lipid with hexane, 2) evaporation of the hexane, 3) emulsification of dried lipid with a aqueous solution of bile salts and 4) isolation of the pure micellar fraction from the emulsion by ultracentrifugation. A review article summarizes difficulties with bile salt micelle sizing due to complex secondary aggregation effects (*See Advances in Colloid and Interface Science*, 26 (1986) 131-154), leading to Applicant's conclusion that methods for the production of small (sub-50 nm) particles are not taught by these references. Applicant further notes that these references do not disclose methods for incorporating stabilizing polymers comprising a cell recognition function.

With respect to stabilization of gas-filled vesicles using biocompatible polymers, Unger et al. teaches, at Col 30, line 18, methods disclosed in U.S. Patent 5,205,290 for methods of making such vesicles (see Col 31, Line 49). U.S. Patent 5,205,290 is directed towards microspheres ranging from 1 to 1000 microns with heat expansion described as a preferred synthesis (Col 3, Line 48 of '290). No particles of less than 2 μm are presented. Accordingly, '290 only enables particles ranging from 2 microns to several hundred microns and thus do not anticipate the sub 50-nm particles of the present invention.

With respect to Unger et al.'s disclosure of several references regarding methods of preparing polymer vesicles (column 72, line 21), a review of these references shows that they teach particles of 1 to 100 microns in size. See Accompanying Declaration. The smallest particles are from Deasey, PB, Microencapsulation and Related Drug Processes (1984) ppg 195-240, Marcel Dekker, New York and Basel. In this reference, 200 nm protein particles are described for albumin spheres which showed aggregation considered useful for stimulating phagocytosis by the reticuloendothelial system (p 227).

Unger et al. also cites an additional four patents as references for vesicle compositions formulated from proteins in Col 22, line 14, namely, U.S. 4,572,203; 4,718,433; 4,774,958; and 4,957,656. As discussed in the accompanying Declaration, the protein particle vesicles as described in these patents are greater than 1 μm.

At Col. 61, lines 12-67, various methods for preparation of liposomes are described. Applicant submits that these methods for preparation of liposomes do not teach methods which will result in the particles of the instant invention, for the reason that the particles of the instant invention are made up of a bioactive component as a core, a surfactant, and polymers with

specific cellular or tissue uptake function, the particles having an average diameter of less than about 50 nanometers. For example, in US 4,921,706 (to Roberts et al) , liposomes of a nanometer size range are disclosed (for example, Col. 6, lines 55-57, and Col. 9, lines 10-13) . However, these particles do not include a polymer with specific cell or tissue uptake function and therefore these liposomes, and methods of making them, do not enable or teach methods which will result in the instantly claimed (made up of a bioactive component as a core, a surfactant, and polymer with a specific cellular or tissue uptake function, and having an average diameter of less than about 50 nanometers).

Further to Applicant's argument, it is submitted that for at least one of the starting materials taught by Unger et al.,particles of a size as claimed in the instant claims (i.e., having an average size of under 50 nm) cannot be obtained. Specifically, Unger et al. teaches various additional or auxiliary stabilizing materials including polysorbate 80 (Tween 80, Col 34 line 3) as capable of providing the Unger et al. particles. In contrast, the instant application teaches at Example 1 that Tween 80 will not result in particles made up of a bioactive component as a core, a surfactant, and polymers, and having an average diameter of less than about 50 nanometers. Further, for Example 11 of '819, it is noted that Tween 20, a polysorbate that is highly related to Tween 80, is used to produce the Unger et al. particles, and as discussed above, the resultant particles are far larger than the inventive particles, i.e., between 3 and 15 microns.

This discussion of the references cited by Unger et al. supports Applicant's teaching that Applicant's particles, as claimed, having sizes less than 50nm in average diameter, are not achievable by prior art methods, instead requiring Applicant's novel methods of manufacture. For example, in one embodiment, Applicant uses water miscible solvents that can be diluted out and simply washed away to create a hydrophobic phase without inducing aggregation of the nascent micelles as compared to the traditional evaporation step used in the preparation of inverted micelles. See Examples.

Thus, given the lack of disclosure of any methods in Unger et al. that are known to those skilled in the art, to result in the instant particles (made up of a bioactive component core, a surfactant, and polymer with specific cellular or tissue uptake function, having an average diameter of less than about 50 nanometers), it is respectfully submitted that undue experimentation on the part of a skilled artisan would be required to arrive at the instantly claimed particles starting from the disclosure of Unger et al. Accordingly, it is submitted that the

portion of the Unger et al. disclosure with respect to sub-50 nm particles is not an enabling disclosure. Unger et al. is thus not a proper reference under 35 U.S.C. § 102(e). Reconsideration of the rejection of claims 66, 67, 87, 88, 90-92, 94, and 101 and allowance of new claims 135-136 is respectfully requested.

(c) *Not all of the elements of the instant claim 135 are disclosed in Unger et al.*

(i) Unger et al. does not teach surfactants in a monolayer structure as claimed in claim 135.

For anticipation under 35 U.S.C. § 102(e), the reference must teach every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987).

Applicants, in this argument, respectfully direct the Examiner's attention to new claim 135, which includes the limitation that the surfactant is associated with a bioactive component in a monomolecular layer. Support for the instant claim amendment can be found at Specification, page 16, lines 10-16.

Applicant's invention, as claimed in Claim 135, is directed to a surfactant associated with a bioactive component in such as manner that the surfactant is associated with a bioactive component in a monomolecular layer. In contrast, Applicant submits that where Unger *et al.* teaches lipid compositions, such lipid compositions are in the format of a bilayer of lipid molecules. In order to help the Examiner properly appreciate the distinction that the Applicant is drawing, Applicant will briefly review the scientific definitions of monolayer surfactants and bilayer surfactants.

By way of brief review, scientifically, lipids, including surfactants, under the proper conditions, may form micelles. An art-recognized definition of "micelles" is the following: "aggregates of surfactant molecules or ions in solutions. Such aggregates form spontaneously at sufficiently high surfactant concentration, above the critical micelle concentration." " *See, e.g.*, THE LANGUAGE OF COLLOID AND INTERFACE SCIENCE – A DICTIONARY OF TERMS (Schramm, 1993)..For ionic micelles, "as the ion[ic surfactant] concentration is increased, the shape of ionic

micelle changes in the sequence spherical-cylindrical-hexagonal-lamellar. For non-ionic micelles, on the other hand, the shape seems to change from spherical directly to lamellar with increasing [ionic surfactant] concentration." *See, e.g.*, MICELLES: THEORETICAL AND APPLIED ASPECTS (Moroi, 1992, Plenum Press NY, pp 45-6).

The term "micelle" properly refers to monolayer structures (i.e., where the lipophilic tails group together and the more hydrophilic or polar head group faces outwards). As can be seen from the illustration below from MICELLES; THEORETICAL AND APPLIED ASPECTS, (Moroi, 1992, Plenum Press, NY, pg 46), the first three depicted micelles are in a **monolayer structure**. The fourth micelle depicted in the below illustration departs from the first three in that it forms a bilayer structure. Such a bilayer micelle is called a lamellar micelle.

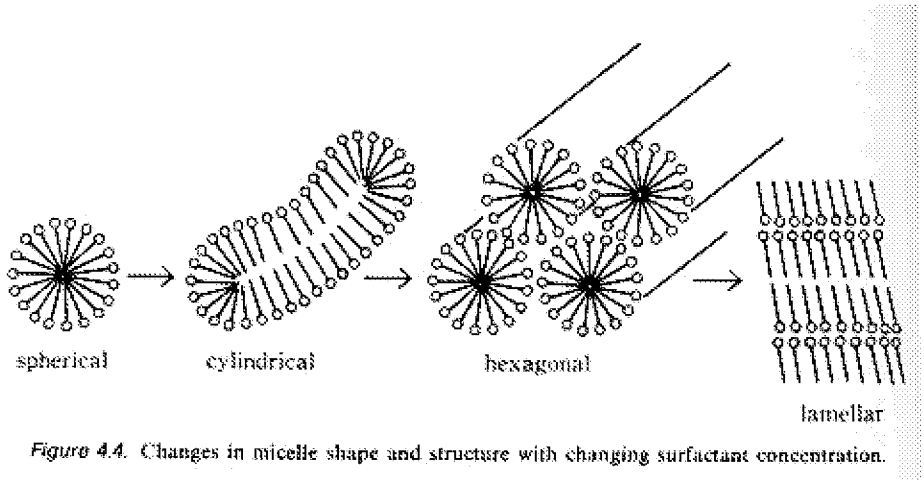

Figure 4.4. Changes in micelle shape and structure with changing surfactant concentration.

The next illustration shows a monolayer micelle as well as a conventional representation of a bilayer micelle geometry. A micelle having a lamellar structure is a **bilayer** and is properly called a vesicle, *see, e.g.*, THE LANGUAGE OF COLLOID AND INTERFACE SCIENCE – A DICTIONARY OF TERMS (Schramm, 1993) ("vesicle: A droplet that is stabilized by the presence at its surface of a lipid **bimolecular** film or series of concentric **bilayers**.").

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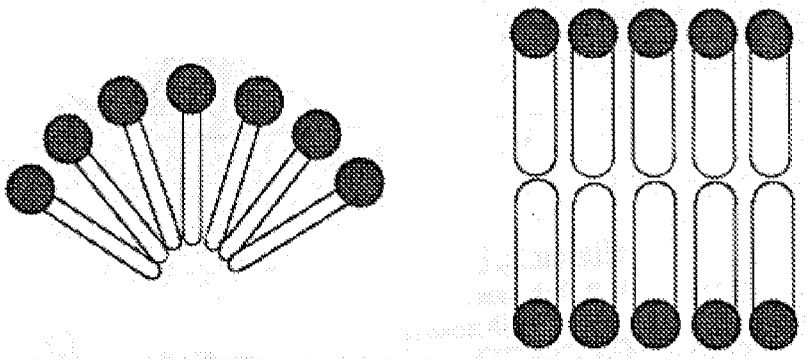

Figure 3.34 Micellar shape determined by the packing of the hydrocarbon chains of a surfactant

Applicant's claim 135 is directed to monolayer micelles, not to bilayer micelles. Claim 135 recites that the surfactant is associated with a bioactive component in such as manner that the surfactant is associated with a bioactive component in a monomolecular layer. This recital limits the claim to monolayer micelles, i.e., non-bilayer micelles. Accordingly, any bilayer structure of a surfactant is excluded from the scope of this claim. In the following discussion, Applicant refers to structures having lamellar micelles as **bilayer micelles**.

Turning to the discussion of claim terms used in Unger et al., Applicant notes that settled Federal Circuit case law shows that claim terms are to be given their ordinary and customary meaning, unless the inventor clearly sets forth a definition that is different from the ordinary and customary meaning(s). *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). Very recent Federal Circuit case law makes it clear that "[w]hen a patentee acts as his own lexicographer in redefining the meaning of particular claim terms away from their ordinary meaning, he must clearly express that intent in the written description." *Merck & Co., Inc. v. Teva Pharms. USA, Inc*, 395 F.3d 1364, 1370 (Fed. Cir. 2005).

The art-recognized definitions of "vesicle" refers to "a droplet that is stabilized by the presence at its surface of a lipid **bimolecular** film or series of concentric **bilayers**." *See, e.g.*, THE LANGUAGE OF COLLOID AND INTERFACE SCIENCE – A DICTIONARY OF TERMS (Schramm, 1993). Vesicles are defined by Schramm to include liposomes. Applicant contends, that to the extent, if at all, that Unger *et al.* teaches that his vesicles and liposomes include monolayers or

monomolecular layers of surfactant, Unger *et al.* is using these terms contrary to the art-recognized definitions of the terms micelle, lamellar micelle, bilayer vesicles, and liposomes and the like.

Per the above-discussed case law, should Unger *et al.* redefine the terms "monolayer", "bilayer", "liposome", and the like contrary to art-accepted definitions, Unger et al. must make this intent clear. Applicant and Attorney for Applicant has carefully reviewed the Unger et al. specification and it is submitted that nowhere in the Unger et al. specification does Unger et al. express any intent to define any terms contrary to art-recognized definitions. It is respectfully submitted that art-recognized definitions should control in the Examiner's understanding of the teachings of Unger et al.

The Unger *et al.* specification is directed primarily towards the preparation of "lipid compositions" comprising vesicles, particularly liposomes, containing gases or low-boiling liquids as gaseous precursors. See issued claims; Col. 6, lines 22-28.

Unger *et al.* defines their term "lipid composition" as "suspensions, emulsions, and vesicle compositions." See Col. 7, lines 21-25. A "suspension" is understood in the art to be defined as a mixture in which fine particles are suspended in a fluid where they are supported by buoyancy. An "emulsion" is defined in the art as an intimate mixture of oil and water, generally of a milky or cloudy appearance. Emulsions may be of two types: oil-in water (where water is the continuous phase) and water-in-oil (where water is the discontinuous phase). Applicant submits that Unger et al.'s teachings with respect to "suspensions" and "emulsions" do not rise to the level of specifically teaching Applicant's monolayer micelles.

With respect to Unger's teachings regarding the structure of vesicles, Unger et al. recites the following: (Col. 7, lines 28-59):

> "Vesicle" refers to a spherical entity which is generally characterized by the presence of one or more walls or membranes which form one or more internal voids. Vesicles may be formulated, for example, from lipids, including the various lipids described herein, proteinaceous materials, polymeric materials, including natural, synthetic and semi-synthetic polymers, or surfactants. Preferred vesicles are those which comprise walls or membranes formulated from lipids. **In these preferred vesicles, the lipids may be in the form of a monolayer or bilayer, and the mono- or bilayer lipids may be used to form one or more mono- or bilayers. In the case of more than one mono- or bilayer, the mono- or bilayers may be concentric. Lipids may be used to form a unilamellar vesicle (comprised of one monolayer or bilayer), an oligolamellar vesicle (comprised of about two or about three monolayers or bilayers) or a multilamellar vesicle (comprised of more than about three monolayers or bilayers).** Similarly, the vesicles

prepared from proteins or polymers may comprise one or more concentric walls or membranes. The walls or membranes of vesicles prepared from proteins or polymers may be substantially solid (uniform), or they may be porous or semi-porous. The vesicles described herein include such entities commonly referred to as, for example, liposomes, micelles, bubbles, microbubbles, microspheres, lipid-, polymer- protein- and/or surfactant-coated bubbles, microbubbles and/or microspheres, microballoons, aerogels, clathrate bound vesicles, and the like. The internal void of the vesicles may be filled with a liquid (including, for example, an aqueous liquid), a gas, a gaseous precursor, and/or a solid or solute material, including, for example, a targeting ligand and/or a bioactive agent, as desired. [emphasis added]

As a first point of argument, it is submitted that Unger et al.'s teachings, where they are directed to lipid compositions (which include surfactants), the lipid compositions comprising vesicles must be in the form of a bilayer structure as is understood in the art. Since vesicles by art-recognized definition are bilayer structures, the skilled artisan will necessarily interpret the term, "monolayer' in Unger et al.'s definition of "vesicle" as referring to a single-walled bilayer micelle. In other words, the term "monolayer", as used by Unger et al., must refer to a single (i.e., only one) bilayer structure. Since a vesicle by definition is a bilayer, the skilled artisan reading Unger et al.'s discussion of "monolayer vesicle' would understand that such vesicles would not include monolayer micelles.

Further, within the quote above, Unger et al. teaches, "unilamellar vesicle (comprised of one monolayer or bilayer), an oligolamellar vesicle (comprised of about two or about three monolayers or bilayers) or a multilamellar vesicle (comprised of more than about three monolayers or bilayers)." The term "unilamellar vesicle" must (by art definition) refer to a structure having a bilayer geometry (i.e., a bilayer micelle). To someone skilled in the art, therefore, the terms "monolayer and bilayer unilamellar vesicles" as used by Unger et al., must refer to one or two bilayer micelles; "oligolamellar vesicles" must refer to two or three bilayer micelles, and "multilamellar vesicles" must refer to more than about three bilayer micelles.

Accordingly, it is submitted that the Unger et al. disclosure with respect to the structure of small surfactant micelles is limited to teachings of "lipid [surfactant] composition[s]" which form "vesicles", known in the art and understood by the skilled artisan as bilayer structures (i.e., bilayer micelles). Accordingly, claim 135, which recites that the surfactant is associated with a bioactive component in a monomolecular layer, is outside the scope of the teachings of Unger et al. Claim 135 is limited to monolayer structures, or monolayer micelles. Accordingly, it is

submitted that not all of the elements of the instant claim are taught by Unger et al. in that Unger et al. does not teach a surfactant in a monomolecular layer. Allowance of new claim 135 is respectfully requested.

Applicants also note that new claim 136 is directed to surfactants selected from the group consisting of 2, 4, 7, 9-tetramethyl-5-decyn-4, 7-diol, molecules containing an acetylenic diol portion, and blends of 2, 4, 7, 9-tetramethyl-5-decyn-4, 7-diol. It is respectfully submitted that Unger et al. do not teach these surfactants. Accordingly, it is submitted that claim 136 is novel over Unger et al. and allowance is respectfully requested.

(ii) Unger et al. teach sizes of 30 nanometers for vesicles only

As discussed more fully hereinabove at part (a)(i), claim 135 is directed to the surfactant associated with a bioactive component in such as manner that the surfactant is associated with a bioactive component in a monomolecular layer. In contrast, Applicant submits that Unger *et al.* teaches a bilayer of lipid molecules in the Unger *et al.* compositions in that Unger et al.'s definition of lipid vesicle compositions, are understood in the art to be bilayer structures (i.e., bilayer micelles).

Turning to Unger et al.'s disclosed sizes of the particles, Unger et al. teaches at Col. 28, lines 48-67, and particularly at lines 51-55, " The size of the vesicles may preferably range from about 30 nanometers (nm) to about 100 micrometers (μm) in diameter, and all combinations and subcombinations of ranges therein." (emphasis added) Accordingly, it is submitted that Unger et al.'s teachings with respect to sub-50 nm particles are limited to vesicles by the plain language of the specification. Vesicles are limited to bilayer structures (bilayer micelles) per the art-recognized definition of vesicle, as discussed above. In contrast, claim 135 is directed to non-bilayer micelles (i.e., monolayer micelles), referring to surfactants in a monomolecular layer.

In the instant claim 135, Applicant teaches particles (made up of a bioactive component core, monomolecular layer surfactant, and biocompatible polymers with a specific cellular or tissue uptake function, having an average diameter of less than about 50 nanometers), in which the surfactant portion is configured in a monomolecular layer (i.e., a non-bilayer micelle). In contrast, Unger et al. teach that the 30 nm sizes are achieved by "vesicles." As discussed hereinabove, Applicant's surfactant is not a "vesicle" since it is not in a bilayer form.

Accordingly, it is submitted that not all of the elements of the instant claim 135 are taught by Unger et al., for the reason that Unger et al. does not teach the small size range of the particle comprising a surfactant in a monomolecular layer. Allowance of new claim 135 is therefore respectfully requested.

CLAIM REJECTIONS UNDER 35 U.S.C. § 103(a)

The Examiner has rejected claims 66, 67, 87, 88, 90, 92-94, 101, 133, and 134 as being unpatentable over Unger et al. (U.S. Patent No. 6,139,819) as applied to claims 66, 67, 87, 88, 90-92, 94, and 101 above, in view of Schneider et al. (FEBS Letters, 1998, 429:269-273). The Examiner contends that Unger et al. does not teach tenascin (the subject matter of claims 133 and 134) or a critical micelle concentration of about 200 micromolar (the subject matter of claim 89).

As a first matter, Applicant would like to clarify that claim 93 is listed as rejected for obviousness, and it was not rejected as anticipated by Unger et al. Claim 93 is directed towards a composition further comprising a water-miscible solvent or a combination of water-miscible solvents. However, it is not argued by the Examiner that Schneider et al. teaches water-miscible solvents or a combination of water-miscible solvents. It is therefore submitted that claim 93 is free of the prior art cited by the Examiner and indication of the allowability of claim 93 is therefore respectfully requested.

According to MPEP § 2142, "[i]n order to establish a prima facie case of obviousness, three basic criteria must be met. First there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available in the art, to modify the reference or to combine reference teachings. Second there must be reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations," *citing In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

First, as discussed above, it is well established that all of the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981 (CCPA 1974). As discussed extensively above in Applicant's section devoted to traversing the Examiner's rejection under 35 U.S.C. § 102(e), and incorporated by reference into Applicant's arguments to the 35 U.S.C. § 103 rejections, Applicant respectfully submits that not all of the elements of the invention as claimed in claims 66, 67, 87, 88, 90-92, 94, and 101 are taught or suggested by Unger et al., and furthermore, claims 66, 67, 87, 88, 90-92, 94, and 101 are not enabled. For example, in

Applicant's above arguments, Applicant contends that given the lack of disclosure of any methods in Unger et al. that are known to those skilled in the art or disclose how to make a particle which includes a surfactant, a bioactive component, and polymer with specific cellular or tissue uptake function having an average diameter of less than about 50 nanometers, it is submitted that the portion of the Unger et al. disclosure with respect to sub-50 nm particles is not an enabling disclosure. Further, Unger et al.'s disclosure of a range that "touches" or "overlaps" the claimed range does not anticipate the claimed 50 nm average size particles.

Accordingly, Applicant submits that given the deficiencies of the Unger et al. reference in terms of disclosing or teaching all of the elements of claims 66, 67, 87, 88, 90-92, 94, and 101, the combination with Schneider et al. (teaching a ligand for targeting tenascin or tenascin as a ligand) does not remedy the lack of teaching in Unger et al. because Unger et al. fails to teach how to make a particle which includes a surfactant, a bioactive component, and polymer having an average diameter of less than about 50 nanometers, as required by the instant claims.

Additionally, Applicant respectfully points out that the methods disclosed by Unger specifically for producing particles comprising proteins result in protein particles having a minimum size of 200 nm in diameter (see, e.g., Example 39A). Although one of ordinary skill in the art might possibly, by the methods taught by Unger et al., prepare tenascin particles, the particles would necessarily be of about 200 nm or greater. Such particles would be outside the scope of the instant claims. Accordingly, Applicant respectfully submits that the combination of the references is not proper in that each and every one of the claimed elements is not present in the combination of Unger et al. and Schneider, et al.

Reconsideration is respectfully requested.

Additionally, even if all of the elements of the instant claims are present in the cited references, (which Applicant does not admit), there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available in the art, to modify the reference or to combine reference teachings AND there must be reasonable expectation of success. Applicant submits that these tests for obviousness fail as well, as applied to the instant claims. The Examiner states that it would have been obvious to make the particles of Unger et al. using tenascin as a targeting moiety with the intent to target the particles to $\alpha 9\beta 1$-expressing cells, with a reasonable expectation of success, since Schneider et al. teach that tenascin is a ligand for $\alpha 9\beta 1$ integrins. Assuming, *arguendo*, that the combination of the references suggest

the instant particles, (which Applicant does not admit), Applicant submits that a reasonable expectation of success from the suggestion of Schneider et al. as tenascin as the targeting ligand is not achieved, for the below reasons.

Although, one may possibly attempt incorporating tenascin as taught by Schneider et al. into liposomal particles, success is not at all predictable. First, it is submitted that protein binding to a target, such as, for example, tenascin binding to its receptor, is highly dependent on correct folding of the protein (its three dimensional structure). Further, the active site required for binding to the target must be available for binding, i.e., present on the accessible portion of the protein. Accordingly, in order for tenascin to function properly to bind to its receptor while incorporated in an instant particle comprising a bioactive core, surfactant, and tenascin, the tenascin will need to be in the correct three dimensional configuration as to present its active site on the exterior of the particle. It is known in the art that proteins are subject to misfolding, aggregation, and denaturation in expression systems and/or upon purification or manipulation. Therefore, it is submitted that success with a tenascin protein as the targeting moiety in the particles of the instant invention is not at all assured.

However, Applicant unexpectedly found success using tenascin as a targeting moiety. Applicant has generated data (See Example 6) showing that topically-applied particles incorporating tenascin as the coating basis were able to effectively target tumor cells containing tenascin receptor, by showing that the particles' DNA (encoding Green Fluorescent Protein, "GFP") was in fact delivered to the tumor cells and expressed by the tumor cells located 5-8 millimeters within an organ-cultured skin biopsy. Demonstration that Applicant's tenascin particles are targeting tumor cells in tissue and not just viable cells can be found by comparing with Example 5, where Applicant's particles coated with hyaluronan were demonstrated to target basement keratinocyte cells and blood vessels in a similar organ-cultured biopsy. Such success was not at all assured or predicted.

Reconsideration is respectfully requested.

With respect to the Examiner's contention that Applicant's limitation that the surfactant has a critical micellular concentration of less than about 200 micromolar (claim 89) is obvious to try, and that it is generally not inventive to discover the optimal working conditions of a prior art method and thus is identified by routine experimentation, Applicant traverses. Example 1 shows a number of non-working compositions, i.e., compositions that completely failed to generate

particles of less than 50 nm that were effective to effectuate transgene production in CRL-1764 rat fibroblast cells (Table 1A). As can be seen, all of the surfactants with a CMC greater than 200 micromolar (identified as parts per million "ppm" in the table) failed to generate functional particles. See samples S, T, U, W, V of Table 1A. Applicant submits that therefore, it is not mere "optimization" that Applicant carried out, as particles not having a surfactant with a CMC of less than 200 micromolar were completely non-functional. The Applicant's results that the sub-200 micromolar CMC surfactants resulted in the functional particles as currently claimed was a true inventive discovery.

Reconsideration is respectfully requested.

Finally, even if the Examiner does not accept Applicant's above arguments traversing obviousness and continues to conclude that a *prima facie* case of obviousness is merited, despite Appliant's above arguments to the contrary, Applicant submits that a *prima facie* case is rebutted because the claimed compounds have unexpectedly advantageous or superior qualities. See MPEP § 2144.09; *In re Papesch*, 315 F.2d 381 (CCPA 1963); *In re Wiechert*, 370 F.2d 927 (CCPA 1967). Applicant has found evidence of unexpected results with Applicant's 50 nm particles as opposed to the prior art particles, rebutting any *prima facie* case for obviousness for the instant claims. Specifically, in Example 3, cells were treated with liposome complexes, dendrimer complexes, Applicant's inventive particles ("nanocapsules") and a positive control. Unexpectedly, it was observed that the use of Applicant's inventive particles reduced the fraction of apoptotic cells in fibroblast cultures by 3 to 100 fold as compared to standard sized (larger) particles. Also surprisingly, Applicant's Example 2 shows that as compared to standard polyplexes of DNA and PEI and lipoplexed plasmid DNA, Applicant's particles shifted pinocytotic activity to caveolae and avoided lysosome co-localization at 10 hours, resulting in improved for improved uniformity of uptake and prolonged effectiveness as compared to larger particles.

Applicant submits that Applicant's inventive particles demonstrated ability to mediate uptake through caveolae, thus avoiding lysosomes within the cell, is truly an inventive finding. It is known that the greatest impediment to successful gene expression via non-viral delivery vehicles is lysosomal degradation: "[r]egardless of the targeting ligand employed, receptor-mediated internalization results in the sorting of complexes toward lysosomal degradation . . . Endosomal sorting toward the lysosomal degradation fate is thus believed to be the greatest

barrier for successful gene expression via non-viral delivery vehicles." CM Varga et al., "Receptor Mediated Targeting of Gene Delivery Vectors: Insights from Molecular Mechanisms for Improved Vehicle Design, Biotechnology and Bioengineering: 70(6) 593-605 (2000). Accordingly, Applicant's particles, which avoid the lysosomal degradation which reduce the effectiveness of non-viral delivery vehicles, provide significant and unexpected results over conventional particles.

Reconsideration is respectfully requested.

For the reasons set forth above, Applicant respectfully submits the claims as filed are allowable over the art of record and reconsideration and issuance of a notice of allowance are respectfully requested. If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefor to deposit account No. 19-5117, if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to deposit account No. 19-5117.

Respectfully submitted,

/Mary Breen Smith/

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